REMARKS

Claims 1-25 are pending in the instant application. Claims 1-6 and 8-12 have been amended. These amendments do not introduce any new matter, and support for them can be found in the specification. Claims 16-21 and 23-24 have been canceled as they are drawn to non-elected subject matter. Claims 22 and 25 have also been canceled. After entry of this amendment, Claims 1-6 and 8-15 will be pending.

Applicants note that the Examiner has made reference to Claims 26-29. Applicants do not believe that Claims 26-29 were filed with the instant application, thus have not specifically cancelled them.

Rejection of Claims 22 and 25 under 35 USC §112, first paragraph

The Examiner has rejected Claims 22 and 25 under 35 USC §112, first paragraph, for lack of enablement. Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have canceled Claims 22 and 25. In light of these cancellations, this rejection should be rendered moot.

Rejection of Claims 1-15, 22 and 25 under 35 USC §112, second paragraph

The Examiner has rejected Claims 1-15, 22 and 25 under 35 USC §112, second paragraph, for allegedly failing to particularly point out and distinctly claims the subject matter which Applicants regard as the invention. Specifically, the Examiner has objected to the term "N-oxide derivatives" in the claims. Without conceding the correctness of the Examiner's argument, but to advance the prosecution of the instant application, Applicants have amended Claims 1-6 and 8-12 to remove the term "N-oxide derivatives." Claims 22 and 25 have been canceled. In light of these amendments and cancellations, this rejection should be rendered moot.

Rejection of Claims 1-4, 7, 9-15, 22 and 25 under 35 USC §102(e)

The Examiner has rejected Claims 1-4, 7, 9-15, 22 and 25 under 35 USC §102(e) as being anticipated by US Patent No. 7,012,075 (Prasit *et al.*). The Examiner cites specific compounds disclosed in Prasit, *et al.*, and states:

> These compounds directly anticipate applicant's claims of a compound of formula wherein R^1, R^2, R^3 are hydrogen, R^4 is C_{1-6} alkyl, X is O, R^7 and R^8 are hydrogen,

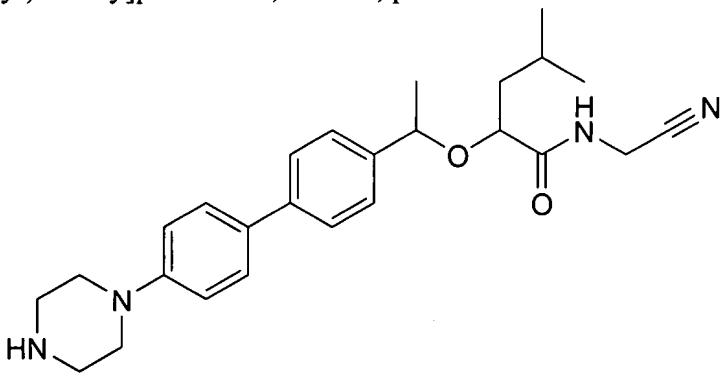
D is aryl or C_{3-8} cycloalkyl, n is 2 and R^9 is hydrogen, C_{3-8} cyclooalkyl or heterocycloalkyl.

Applicants have amended the definition of R^7 to delete hydrogen. Thus, Claims 1-4, 7 and 9-15 are no longer anticipated by Prasit, *et al.* In light of these amendments, this rejection should be rendered moot.

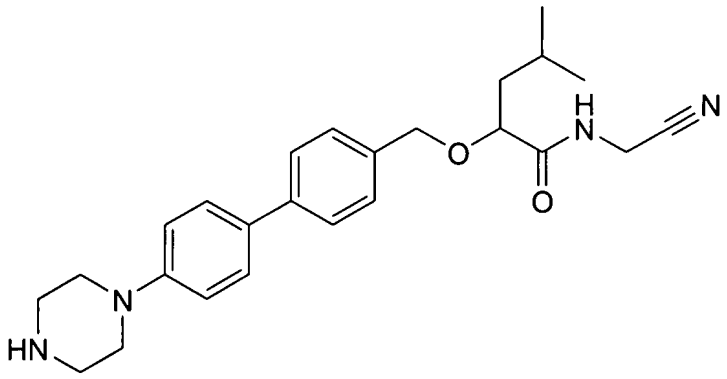
Rejection of Claims 1-4, 7, 9-15, 22 and 25 under 35 USC §103(a)

The Examiner has rejected Claims 1-4, 7, 9-15, 22 and 25 as being upatentalbe over Prasit et al. Specifically, the Examiner states:

> The difference between the prior art of Prasit et al and the instantly claimed compounds of Claims 1-4, 7, 9-15, 22 and 25 (see for example N-(cyanomethyl)-4-methyl-2-[1,(4'-piperazin-1-yl-1,1'-biphenyl-4-yl)ethoxy]pentamide, line 14, p.101



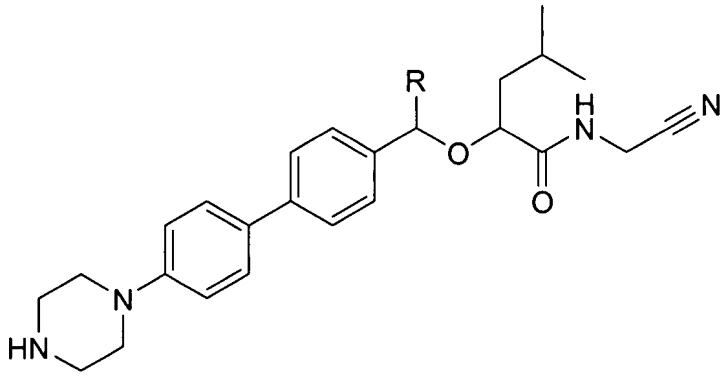
> is that the inventions of Prasit et al is directed to compounds wherein the R^7 or R^8 (as defined in the instant claims) represents a hydrogen atom rather than R^7 or R^8 = alkyl, such as methyl, that is claimed in the instant invention.
>
> Prasit et al is analogous art because the compounds of the structural formula:

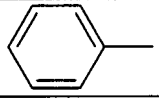
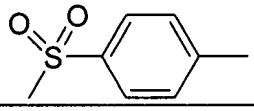
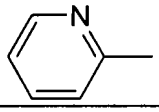


wherein the R^7 or R^8 (as defined in the instant claims) is hydrogen, rather than an alkyl group such as methyl, would be considered analogous art. As stated in In re Wood, 199 USPQ 137, hydrogen and methyl are deemed obvious variants, and substitution of a methyl for the hydrogen in the R^7 or R^8 position of the compounds of Prasit et al would give rise to the compounds of the instant claims. *In the absence of unexpected results*, one skilled in the art would expect that the instant claims which are directed to compounds found to be inhibitors of cathepsins are analogous to the compounds of Prasit et al, i.e. adjacent homologues such as where R^7 or R^8 = H rather than Me, is prima facie. (*emphasis* added)

Applicants respectfully traverse the Examiner's rejection. The instant invention provides cathepsin K inhibitors that **require** substitution at the R^7 or R^8 position. The cathepsin K inhibitors disclosed in Prasit et al **do not** provide for substitution at the R^7 or R^8 position.

Applicants submit that the present invention cannot be considered obvious over the prior art (Prasit et al) because the compounds of the instant invention have several unexpected advantages over the prior art. First, by substituting the R^7 or R^8 position with a non-hydrogen substituent, the potency of the compound greatly increases. When measured in an assay with humanized rabbit cathespin K (which is nearly identical to human cathepsin K), substitution provides very potent compounds, most displaying subnanomolar affinity. Second, substitution at the R^7 or R^8 position improves the selectivity of the compound against Cathepsin L. This improved profile can be observed in the following table:



R	Humanized Rabbit Cathepsin K IC_{50} (nm)	Selectivity factor versus Cathepsin L
H	2.6	225x
Me	1.5	895x
	0.022	33600x
	<0.16	>1245x
	0.21	950x

Applicants have chosen representative compounds to demonstrate their points, including two of the structures relied on by the Examiner in the rejection (wherein R is H and R is Me). Data from more compounds can be provided, or the same data can be provided in a declaration, if necessary.

The first compound, wherein R is H, was disclosed in Prasit et al., and cited by the Examiner. This compound has an IC_{50} of 2.6 nm against cathepsin K protein. When a non-hydrogen substituent is added, the compound's potentcy increases; for example, substituting with a methyl group increases the potency to 1.5 nm, and substituting with a phenyl group increases the potency to 0.022 nm.

Likewise, when R is H, the compound is 225 times as selective for cathepsin K versus cathepsin L. When a non-hydrogen substituent is added, the compound's selectivity increases; for example, substituting with a methyl group increases the selectivity to 895x, and substituting with a phenyl group increases the selectivity to 33600x.

The improved potency and selectivity observed by providing non-hydrogen substitution at the R^7 or R^8 position is neither taught nor suggested by Prasit et al. After reading the disclosure in Prasit et al., one skilled in the art would not expect to observe the improved profile possessed by the compounds of the instant invention. Accordingly, Applicants respectfully request that the rejection of Claims 1-4, 7, 9-15, 22 and 25 under 35 USC §103(a) be withdrawn.

Claim Objections

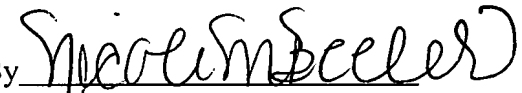
The Examiner has objected to Claim 25 as being a substantial duplicate of Claim 22. Applicants have cancelled Claim 25. The Examiner has also objected to Claims 5-6 and 8 as being dependent upon a rejected base claim. Applicants have amended Claim 1 (base claim), and believe that the Examiner will find Claim 1 allowable. Accordingly, Applicants respectfully request that the claim objections be withdrawn.

Specification Objection

The Examiner has objected to the content of the specification because it does not contain a cross reference to related applications section. Applicants have amended the specification to include a cross reference to related applications section. Thus, this objection should be rendered moot. Accordingly, Applicants respectfully request that the specification objection be withdrawn.

If a telephonic communication with the Applicants' representative will advance the prosecution of the instant application, please telephone the representative indicated below. Applicants believe no additional fees are due but the Commissioner is authorized to charge any fees required in connection with this response to Merck Deposit Account No. 13-2755.

Respectfully submitted,

By 

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Date: April 16, 2007